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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/697,329	10/27/2000	Eiichi Iishi	1422-449P	8402

7590 04/13/2006

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EXAMINER	
HABTE, KAHSAY	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 04/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/697,329	IISHI ET AL.	
	Examiner	Art Unit	
	Kahsay Habte	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 7 and 12-18 are pending in this application.

Response to Amendment

2. Applicant's amendment filed 1/20/2006 in response to the previous Office Action (7/22/2005) is acknowledged. Rejection of claims 7 and 12-17 under 35 U.S.C. 103(a) (item 3) has been maintained. Rejection of claims 16-17 under 102(b) and the second paragraph rejection item has been obviated by the amendment. Applicant's amendment also raises new issues that need further rejection.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7, 12-15 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaspersen *et al.* {Journal of Label. comp. and Radiopharm., 27, No. 9, 1055 (1989)} in view of Khankari et al. {Thermochemica Acta 248 (1995) 61-79}. Kaspersen et *al.* teaches the multi-step synthesis of Org-3770 (mirtazapine) on page 1058 (Fig.4). On page 1066, Kaspersen *et al.* teaches the synthesis of mirtazapine and the crystallization of the mirtazapine (compound **1c**) from the crude product using

methanol/water solvent mixture to achieve colorless crystals. The only difference between applicant's mirtazapine hydrate and Kaspersen's Org-3770 hydrate is that Kaspersen's hydrate is ^{13}carbon labeled, but the instantly claimed product requires that the mirtazapine be unlabeled. The structure of Kaspersen's mirtazapine and the structure of applicants unlabeled mirtazapine are extremely closely related. Just as the labeled compound clearly suggests the unlabelled so do the labeled hydrate clearly suggest the unlabelled hydrate. This is particularly true since the labeled compound was prepared in order to study what the known unlabelled compound does in the body. As shown in Khanakari et al., hydration alters pharmaceutically important properties such as solubility and the physical and chemical stability of pharmaceutical solids that contributes in the modification of bioavailability and product performance (see page 64). It is obvious to one skilled in the art to modify the labeled Kaspersen's mirtazapine hydrate to a hydrated unlabeled mirtazapine compound, since hydration alters the physical chemical or biological performance of a pharmaceutical drug (e.g. bioavailability, solubility, stability) and the fact that hydrates are a conventional form of making a pharmaceutical composition as shown in Khanakari et al. (see page 77, last paragraph). Thus, the prior art teaching that mirtazapine forms a hydrate in the labeled form would suggest that mirtazapine forms a hydrate in the unlabelled form, since one expects that labeled and unlabeled to have the same physical properties. One is motivated to prepare this unlabeled hydrates because (1) drugs are normally administered in their unlabelled form (which is the form that mirtazapine is commercially available in) and (2) the hydrate is a standard pharmaceutical form as is shown by the

secondary reference. Thus, the teaching that mirtazapine (albeit labeled) forms a hydrate would provide the motivation for preparing the unlabeled mirtazapine in a hydrate form for pharmaceutical use.

Response to arguments

Applicants arguments filed 1/20/2006 have been fully considered but they are not persuasive.

Applicants argue, "Kaspersen et al. do not disclose or suggest that the labeled compound is a hydrate.....Applicants respectfully request that the Examiner refers to the mirtazapine compound of Kaspersen et al. in the future without using the term hydrate." The examiner disagrees with applicant's argument. The compound is asserted to be inherently a hydrate because it is made via a method which applicants use to prepare hydrate.

According to MPEP 2112.01:

*Where the claimed and prior art products are identical or substantially identical in*structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). *[underscoring added]*

Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Applicants also argue, "A person skilled in the art is well aware that the *chemical* properties of the labeled compound are substantially the same as those of the unlabeled compound, and the *physical* properties of the labeled compound are different from those of the unlabeled compound.....Therefore, the difference between the molecular weight of the labeled compound 1c and that of the unlabeled compound is 6. This great difference of the molecular weight makes the physical properties of the unlabeled compound different from those of the unlabeled compound." The examiner disagrees with applicants. Applicants are speculating the physical characteristics of the labeled and unlabeled compounds and reached a conclusion that "even if the labeled compound is hydrate (which Applicants do not concede), it cannot be expected from the labeled compound by a person skilled in the art that the unlabeled compound would be a hydrate, because the molecular weight of the labeled compound is greatly different from the unlabeled compound". Applicants have to compare hydrates of the labeled and unlabeled compounds and present the data in a declaration form to overcome portion of the obviousness rejection.

The claimed invention is drawn to a hydrated unlabeled mirtazapine crystals and use of said hydrated unlabeled mirtazapine crystals for the treatment of depression. The obviousness rejection is based on Kaspersen's in view of Khanakari et al. that

teaches the advantages of hydration in pharmaceutical compositions. Note that Kaspersen labeled compounds were prepared for metabolic studies in animal and man for the determination of the bioavailability. According to page 1055, Kaspersen's hydrated mirtazapine are tested as a potential antidepressant as the utility of the claimed invention.

In regard to applicant's argument: "Kaspersen et al. do not disclose or suggest that the obtained compound is a hydrate. Accordingly, it is illogical to take from the disclosure of Kaspersen et al., that Kaspersen et al. made the hydrate as asserted by the Examiner". The examiner disagrees with applicants. For more details see the discussion above and also MPEP 2112.01. The compound is asserted to be inherently a hydrate because it is made via a method that applicants use to prepare hydrate.

Applicant's conclusion in regard to similarity of methods "it cannot be expected with confidence by a person skilled in the art that both unlabeled compound and labeled compound would generate a hydrate in the same way", and in regard to IR data "if Kaspersen et al. had in fact made the hydrate, it is reasonable to presume that Kaspersen et al. would have mentioned it in the description or in the list of peaks for the IR". Applicants are again speculating the method of making hydrates from labeled and unlabeled compounds. The only means to reach such conclusion is to carry out the method and present the data in a declaration form. The same is true for the hydrate IR peaks that are not present in Kaspersen et al. as argued in previous Office Action. Many IR data reports only important peaks are reported and usually peaks from water

or other weak peaks are ignored. The peaks are not usually reported because they are very broad or they are not important because they are not part of molecule. Thus, applicant's argument that the IR-spectrum described by Kaspersen et al. do not include a peak around 3000 cm^{-1} is not persuasive. Additionally, the examiner is providing six US Patents (5,284,857; 5,401,753; 5,397,790; 5,583,149; 4,524,146 and 5,468,768) as an evidence to rebut applicant's argument. In said US Patents, that disclose different type of hydrates the water peak around 3000 cm^{-1} was not reported when the IR data was taken using KBr that is the same as Kaspersen. Specifically, in US Patents 5,583,149 and 5,468,768 (column 17, lines 30-38 and column 17, lines 16-21) the IR(KBr) peaks for the hemifumarate hydrate compound were reported as 1660, 1575 and 1375 cm^{-1}. In US Patent 5,397,790 (column 14, EXAMPLE 23), the IR(KBr) peaks for the hemihydrate product were reported as 1790, 1670 and 1600 cm^{-1}. Similarly, in US Patent 5,401,753 (column 12, EXAMPLE 18) for one-quarter hydrate of the title compound (n =1/4) the IR(KBr) peaks were reported as 1780, 1665 and 1610 cm^{-1}. A hydrate product of the pyrazolo[4,3-c]quinoline derivative in US Patent 4,524,146 (column 9, EXAMPLE 2), the IR(KBr) peaks were also reported as 800, 829, 870 and 880 cm^{-1}. A quarter hydrate product (n =1/4) in US Patent 5,284,857 (column 30, EXAMPLE 96) were also reported with an IR(KBr) peaks at 1667, 1658, 1638, 1613, 1600, 1568 and 1476 cm^{-1}. Note that the hydrates of said US Patents do not contain any IR(KBr) peaks at around 3000 cm^{-1}. It may be conventional to ignore peaks not part of the base molecule, or the water peak may have been broadened to the point where it was not seen, especially if the water amount was small.

Note that both applicants and Kaspersen use an extremely similar method, thus, it is presumed that the same hydrate product is formed from virtually the same crystallization method. Kaspersen *et al.* on page 1066 teaches the synthesis of mirtazapine and the crystallization of the mirtazapine (compound **1c**) from the crude product using charcoal, methanol/water solvent mixture to achieve colorless crystals. Applicants on page 6 (lines 5-6) also discloses mixed solvents such as methanol/water, plus charcoal to make crystals of a mirtazapine hydrates. The only difference between applicant's mirtazapine and Kaspersen's Org-3770 is that Kaspersen's compound **1c** is ^{13}carbon labeled, but the instantly claimed product requires that the mirtazapine be unlabeled. One skilled in the art would presume that labeled and unlabelled would crystallize in the same way.

Applicants and Kaspersen use almost the same method to prepare crystal of mirtazapines, thus, it is obvious that these two have the same characteristics (i.e. hydrates). The examiner has established reasonable grounds that Kaspersen's mirtazapine product as a hydrate (see above

Since the hydrate of the labeled compounds could just as well be important intermediates for preparing anhydrous labeled mirtazapine crystals and the fact that the hydrates are the conventional way of making pharmaceutical formulation as shown above, the obviousness rejection is proper.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In claim 16, the term "solid" is a new matter. Applicants have added "solid" to overcome a prior art rejection. Originally, claim 16 recite "a pharmaceutically acceptable composition" but amended claim 16 now recites "a pharmaceutically acceptable solid composition". Applicants indicate support for this in the entire disclosure of the present specification, but "solid composition" is not disclosed in the specification.

5. Claims 16-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for n = 2-5, does not reasonably provide enablement for n =1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. According to the specification (Example 1), the water content reported is 2.3%. According the Communication of a Notice of Opposition to EP 1225174 by Teva Pharmaceutical Industries (pages 3-4, submitted on 3/4/2005) that is part of the disclosure in this case, the water content 2.3% corresponds to n = 2.88

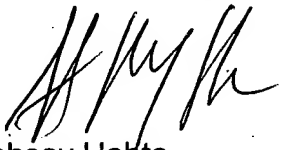
(non-integer). In this communication, there is an Affidavit by Professor Micheal B. Hurthouse as evidence that it is physically impossible to form the monohydrate crystal (n=1). Thus, claim 17 covers an embodiment, which does not exist. Since there is no description how use specific hydrates for the method of treatment falling within the scope of claim 17 (i.e. n= 1), the enablement rejection is proper.

Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson (Acting SPE) can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kahsay Habte
Primary Examiner
Art Unit 1624

KH
April 11, 2006